further depress the patient whose symptoms are due to barbiturates or other depressants.

Naloxone will promptly (within 1 to 2 minutes) and dramatically reverse the respiratory depression but its antidotal action lasts only 2 to 3 hours. The depressant effects of the narcotic-like drugs last from 24 to 48 hours. Therefore it is important to monitor the patient continuously during this period and administer repeated doses of naloxone before serious respiratory depression can reoccur.

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Factors Affecting Lung Maturation

THE IDIOPATHIC RESPIRATORY DISTRESS SYNDROME (IRDS) is a disease of premature infants. It accounts for approximately 25,000 deaths per year in this country. Perhaps the disease should no longer be termed "idiopathic." According to the work of such investigators as Avery, Mead, and Gluck, it appears to proceed from a deficiency of surfactant resulting either from a delay in maturation of the alveolar lining cells producing surfactant or from a defect in release of the substance from the cell.

Using the lecithin sphyngo-myelin (L/S) ratio determination or the bubble stability test on amniotic fluid, it now has become possible to routinely determine the extent of maturation of the human fetal lung. Several conditions including maternal heroin addiction, intrauterine growth retardation, and perhaps amniotic membranes ruptured longer than 16 hours probably cause an accelerated production or release of surfactant.

Liggins showed that maturation of fetal lamb lungs could be accelerated by the antepartum administration of glucocorticoids. Liggins and Howie have published evidence that betamethasone injected into women in premature labor at least 48 hours before delivery decreases the incidence of IRDS in infants born before 32 weeks' gestation. Baden and other investigators in Montreal found no decrease in the incidence of hyaline membrane disease in infants receiving corticosteroid therapy after delivery.

However, more studies are necessary before the routine use of corticosteroids in premature labor can be recommended. In extreme situations, when delivery is inevitable before 32 weeks gestation and the L/S ratio is low or the bubble stability test negative, administration of betamethasone might be considered.

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Hypothalamic Factors

HYPOTHALAMIC NEUROHUMORAL control of pituitary hormone secretion has been established. There are at least nine neurohumors, with three now synthesized. Adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), luteinizing hormone (LH) and follicle stimulating hormone (FSH), are responsive to hormones from target glands which inhibit further secretion by action exerted on the pituitary, the hypothalamus, or both. Hypothalamic inhibitors for growth hormone (GH), melanocytic stimulating hormone (MSH) and prolactin compensate for the absence of negative feedback products from their target organs.

Thyroid releasing hormone (TRH), a tripeptide that has been synthesized, is effective when administered either orally or parenterally. It stimulates TSH and prolactin release and is inhibited by thyroid hormones. Clinically, TRH can be used to differentiate primary hypothalamic and pituitary causes of hypothyroidism, confirm Graves' disease, measure TSH reserve and increase milk production in cows.

Luteinizing releasing factor (LRF), a decapeptide that also has been synthesized, is capable of stimulating- gonadotropic secretions. A specific follicle releasing factor (FRF) has not been identified. The prepubertal hypothalamus is inhibited by low levels of circulating sex steroids. At puberty, steroid-mediated hypothalamic maturation leads to increased LRF production and increased pituitary stores of gonadotropin. LRF stimulation then leads to a heightened release of LH and FSH. Elevated sex steroids can alter pituitary responsiveness to LRF. Clinically, some patients with hypogonadotropic hypogonadism have been found to have a deficiency of LRF rather than of LH or FSH. Prolonged therapy with LRF may be helpful in treating oligospermia and azospermia. An LRF antagonist might be useful in birth control.

Somatotropin release inhibiting factor (SRIF),

a tetradecapeptide recently synthesized, inhibits release of growth hormone and may have clinical importance in the treatment of acromegaly and juvenile diabetes mellitus.

Growth hormone releasing factor (GRF) has not yet been satisfactorily isolated or synthesized.

Corticotropin releasing factor (CRF) may act in conjunction with vasopressin to control ACTH secretion.

Melanocytic hormone releasing factor (MRF) and melanocytic hormone inhibiting factor (MIF) control MSH secretion. If the results of animal experimentation can be duplicated in man, MIF may have clinical applications in parkinsonism and depression.

The secretion of prolactin appears to be under double—prolactin releasing factor (PRF) and prolactin inhibiting factor (PIF)—hypothalamic regulation. Dopamine can decrease prolactin concentration, possibly by stimulating PIF, whereas central nervous system depressants will increase serum prolactin. PIF may have value in inhibiting undesired lactation.

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Side Effects of Diphenylhydantoin in Childhood

SINCE ITS INTRODUCTION in 1938, diphenylhydantoin (DPH) has been an effective anticonvulsant in the treatment of children with generalized and focal motor seizures and, to a lesser extent, psychomotor seizure disorders. Gum hypertrophy, hirsutism, ataxia and rash are among the commonly recognized side effects of DPH. Recent studies have added to the list of known potential side effects. Other investigations have emphasized the importance of its route of administration and its interaction with other medications, as well as the value of measuring DPH serum levels in achieving effective seizure control.

Reports of rickets in children receiving long-term anticonvulsant therapy have suggested that DPH, either alone or in combination with other anticonvulsants, may significantly lower levels of serum 25-hydroxycalciferol, the biologically active form of vitamin D. Therefore, it is probably advisable for children receiving DPH to be periodically screened for rickets by x-ray studies and tests of serum calcium, phosphorus, and alkaline phosphatase. If rickets is shown to exist another anticonvulsant may be cautiously substituted for DPH or small doses of vitamin D can be administered.

The administration of DPH to a pregnant woman may affect the fetus and, therefore, the infant after birth. The risk of an infant's having a significant congenital malformation at birth is two or three times greater than the average when the mother has been given DPH for seizure control during the first trimester of gestation. Serious coagulation defects in newborn children have also been attributed to use of DPH by pregnant women. Depleted clotting factors can be rapidly restored by administration of vitamin K, however.

Following head trauma, DPH and dexamethasone are frequently used simultaneously to prevent post-traumatic seizures and brain edema. However, DPH will hasten the degradation of dexamethasone, requiring the physician to use more steroid to reduce brain swelling. Also, investigators have shown that DPH is probably of little value in suppressing seizure activity in the immediate post-traumatic period. Therefore, the simultaneous administration of DPH and dexamethasone following head trauma is not advised.

The route of administration of DPH is important. The substance crystallizes in muscle depots and causes unpredictable blood levels when it is finally absorbed. Absorption from the gastrointestinal tract is preferred although DPH may be given intravenously if proper precautions are taken.

The effectiveness of DPH is dependent on its serum concentration. Less than 10 μg per ml rarely results in seizure control while levels in excess of 20 μg per ml produce ataxia and slurred speech. The widespread availability of gas-liquid chromatography at many centers has enabled physicians to obtain highly accurate determinations of serum concentrations of DPH. Such experience has shown wide variations in the dose of DPH required in relation to body weight to reach satisfactory therapeutic levels. It is advisable to titrate poorly controlled or overmedicated patients on the basis of their serum DPH levels rather than arbitrary adjustments or selection of an alternate drug. Serum monitoring has also shown that DPH administered orally once a day will satisfactorily